Tissue banking programmes in Europe

Eric S J Kalter and Theo M M H de By
Bio Implant Services Foundation, Leiden, The Netherlands

In Europe, organ centres such as Bio Implant Services (BIS) in cooperation with Eurotransplant, play an intermediary role from donation of tissue and organs to allocation and transplantation. They take responsibility for donor medical/safety screening and organize procurement. Tissue banks are autonomous and are responsible for tissue processing and preservation. Allocation of scarce tissues is performed according to rules set by committees of renowned experts in the field. Most frequently donated types of tissues are corneas, heart valves, bone and soft tissue and skin. In this article, optimal serological screening of the donor, and the banking of these tissues in Europe is reviewed in relation to clinical need and volume of transplantable tissues available, number of banks and their organisational level, methods of explantation, processing and preservation, quality standards and new developments.

In this article, current tissue banking programmes in Europe are described for the banking of eyes, heart-valves, bones and skin. In many countries, tissue banks work together with an intermediary, which takes care of procurement and allocation of tissues. As an example, the process and activities of Bio Implant Services (BIS) are described. Since safety of tissues is of overriding concern, a summary of current state-of-the-art donor screening for transmissible diseases is also given. This review only highlights current developments in the tissue banking areas covered by the activities of BIS and should not be regarded as complete or exhaustive.

Goals and roles for organ centres in Europe

Human tissues are scarce in an absolute and relative sense. In a legal sense, they are included in the definition of ‘organ’. In order to ensure objective allocation, primarily on medical criteria, without commercialization, governments in different countries have recognized the need for so-called organ centres which, amongst other activities, register the report of a donor, procure and allocate organs including tissues. Examples are the Transplant Services Authority (UKTSSA) in the UK, the Etablissement Français des Greffes (EFG) in France, and the
Organización Nacionales de Trasplantes (ONT) in Spain. In The Netherlands, Bio Implant Services Foundation (BIS) is the organ centre for tissues but it cooperates internationally too. It works closely with Eurotransplant, which is the responsible organ centre for vital organs in an area covering countries such as Belgium, Luxemburg, Germany and Austria in addition to The Netherlands. Organ centres concentrate their activities in geographical areas and between these centres regular exchange of data concerning the requests for, and availability of, grafts takes place. Moreover, policies, standards and scientific developments and their implications for the allocation process are communicated regularly to maximize harmonisation.

The role of BIS as organ centre

As already stated, BIS is the responsible organ centre for tissues in The Netherlands. As an example of the working methods of an organ centre, the process and activities of BIS will be described here. The main categories of tissues procured are corneas, heart valves, bone and soft tissue, and skin. Many donors are so-called multi-organ or multi-tissue donors. This means that one donor donates multiple tissues and sometimes also organs, such as kidneys or the liver. Usually, the physician in charge of the deceased patient informs BIS that a will for donation of tissues exists and that a donor is available. A major aspect of the function of BIS is the screening of the medical history of the donor for safety aspects. After donor acceptance, BIS organizes explantation of tissues and transportation to the tissue banks. To this end, blood is withdrawn to perform a serological screening in order to detect transmissible diseases (see below). The number of accepted donors in The Netherlands from 1993–1996 is listed in Table 1.

All cooperating tissue banks are autonomous. They are responsible for proper preparation and preservation of donor tissues. When the tissue is declared fit for transplantation, the tissue bank notifies BIS. BIS plays an intermediary role between tissue banks for all these different tissues and recipients in The Netherlands and Germany and to a lesser extent outside this area. For example, under an agreement with the tissue banks of the Transplant Services Foundation in Barcelona, an exchange with Spain is also ensured. BIS subsequently matches the available graft with the most suitable recipient on the waiting list.
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*Some donors were multi-tissue and/or multi-organ donors, therefore, no totals are given in The Netherlands, mortality rates are approximately 135,000/year.

**Tissue allocation, traceability and tracking**

Allocation criteria are a set of rules which objectively determine which recipient will receive the available graft. For this purpose, an international committee of highly renowned experts, per tissue type, is installed. These allocation rules are reviewed periodically. For example, in the case of HLA-typed corneas, specific allocation rules are applicable. First, the recipient with the best suitable HLA-match is selected. If more than one patient has the same HLA-match grade in comparison to the donor of the cornea, the recipient with the longest waiting time will qualify first. By having donor registration and allocation in the one place, BIS can assure tracking and traceability of the tissues too, which is an important prerequisite in tissue transplantation.

**New developments**

The cooperation between BIS and the tissue banks is aimed at increasing the number of donations and simultaneously improving the quality of grafts and of the allocation process. By improving allocation, it is expected that long term graft survival is influenced positively. To evaluate the allocation criteria, BIS is participating in follow up studies. Data from these studies are the main source for adjusting current allocation schemes. Collaboration in an international framework also implies that the participating tissue banks, together with BIS, strive for an optimal quality standard. Therefore, BIS is also participating in various standardization committees at the national and international level. Moreover, jointly the tissue banks and BIS are able to monitor international developments effectively and, if necessary, able to adequately bring their joint interests to the attention of governmental bodies throughout Europe.
Donor screening

The time available between donation of tissue and its subsequent transplantation in a recipient requires a stringent analysis of risk factors for transmissible diseases. Cornerstones in risk analysis are: donor history for behavioural risk factors, visual inspection for puncture sites and tattoos, serological screening and bacteriological cultures of blood and tissues. Recently, a new version of the uniform Donor Medical History and Behavioral Risk Assessment has been issued by the American Association of Tissue Banks (AATB), and similar listings are being incorporated in various guidelines or standards of tissue banking associations, such as the European Association of Tissue Banks (EATB) and the European Association of Musculoskeletal Tissue Banking (EAMST) in line with the Guidelines for the Prevention of the Spread of Human Immunodeficiency Virus (HIV) of the Centers for Disease Control, published in 1994. It has been argued, however, that very strict guidelines may prevent donation of organs from appropriate donors because of unnecessary broad restrictions and have, therefore, been contested. In the US, between 1988 and 1992, only 7 known cases have been documented where the same donor has transmitted HIV to the recipients, whereas during the same time 66,284 organ recipients were transplanted. The number of false positive results during serological screening is, amongst other factors, related to the presence of hemolysis, the post mortem time of blood sampling and also to the assay procedure used. False negative results are reported to be related to hemodilution and, when the polymerase chain reaction (PCR) technique, is used, to a delay between withdrawal of the sample and the moment of assay. By definition, a window period exists, notwithstanding the appearance of new generations of improved antibody tests. Always a viraemia exists before antibody formation can occur. Therefore, a donor can be infective before seroconversion. The respective windows are currently: for hepatitis B, 59 days (range 37–87 days); hepatitis C, 82 days (54–192 days); and for HIV, 22 days (6–38 days). Also, certain disease states and therapies may interfere with antibody formation and, therefore, a direct demonstration of the viral antigen (viral nucleic acids) by PCR can be very useful in confirming the presence of an active infection in patients with chronic hepatitis, individuals with indeterminate serology, in immunosuppressed patients and in babies, born to seropositive mothers. Theoretically, due to its specificity, a PCR assay may give a false negative result when slight changes in the genome of the virus have occurred and this is currently being investigated. With the application of these PCR techniques, the window for HIV can be reduced to approximately 11 days. The estimated risk for HIV transmission in 'window-phase' blood donations in the US has been...
calculated to be 1 in 493,000 blood donations\textsuperscript{14}. One should, however, take into account that the history of tissue donors can be screened less optimally in comparison to blood donors and, therefore, this risk may be higher in tissue donors\textsuperscript{16}. On the other hand, for Europe, the actual risk that a tissue donor is in the window phase for HIV at the moment of donation is lower than in the US. In European voluntary blood donors, the risk of a window phase HIV transmission has been calculated by the European Plasma Fraction Association study on the basis of approximately 10 million blood donations in 1995 to be 1 in 1.3 million (Lelie PN, personal communication). The ideal tissue donation procedure, therefore, ensures that a thorough history for risk factors is taken and physical examination is performed, that blood is withdrawn and processed in a timely fashion and that the laboratory techniques used are state-of-the-art.

**Eye banking**

**Clinical need**

At the 9th meeting of the European Eye Bank Association (EEBA) in Venice (26–29 January, 1997), a directory was published containing the results of an inquiry\textsuperscript{17}. Together with data from BIS, these numbers form the basis for this section. It is likely that actually many more eye banks collect corneas for local use but the EEBA currently involves 50 eye banks from 23 countries who predominantly use organ culture as the preservation method. Together, these eye banks processed almost 23,000 corneas in 1995, of which 14,000 (60\%) were issued for transplantation. Almost 1550 corneas were allocated through Euro-transplant(ET)/BIS in 1996. Yet, the waiting lists remain and, by the end of 1996, about 800 patients were listed at ET/BIS for a cornea. For random corneas, i.e. not matched for HLA-type, the waiting time is very short in the case of clinical urgency. For example, when a perforation of the cornea exists, a cornea is allocated without delay. For general indications, the mean waiting time for a ‘random’ cornea is about 8 months. In 30\% of the transplants which are allocated through BIS, HLA-typing is performed and the mean waiting time in this group is also 8 months. However, two groups can be clearly distinguished: (i) those with HLA phenotypes which occur regularly in the region served, with a mean waiting time of 3 months; and (ii) those patients with less frequently observed HLA phenotypes, who have to wait for a mean time of 18 months. The average number of HLA mismatches currently is down to 1.13 for HLA A and B, and 1.01 for DR, for the matched
corneas allocated through the BIS Foundation. The allocation rules are set by an international committee of experts (see above). Lamellar tissue is transplanted for anterior corneal diseases and, in exceptional cases, for refractive and reconstructive surgery. Scleral tissue is used as coverage of the acryl ball which is used for filling of the orbita in cases where the eye is removed and in reconstructions of the eye and eyelids. From the response to the EEBA inquiry, it appears that, at least in 1075 transplants in 1995, scleral tissue was used throughout Europe\textsuperscript{17}.

**Explantation**

In most cases, the complete bulbus is removed from the donor and replaced by a prosthesis. An alternative method is to remove only the cornea and to replace this by a contact lens-like cover. However, in cases of elevated central venous and intracranial pressure or when anticoagulants have been given previously to the donor, a danger of haemorrhage exists with both methods. In some countries, the removal of only corneoscleral discs is preferred with regard to legal restrictions. This method, however, may increase infection rates of the donated cornea\textsuperscript{17}.

**Preservation**

Corneas can be preserved by ‘organ culture’, which is performed at around 34°C, and which is used in two-thirds of the banks who responded to the EEBA inquiry\textsuperscript{17}. Another method commonly used is storage at 4°C. Organ culture allows for a longer preservation time, which can be up to 30 days but usually is around 16 days. Cold storage at 4°C can be done up to 7 days and is usually done for a mean duration of 3 days. The most frequent reason to discard corneas is corneal opacity or inadequate endothelium, which occurs in 23% of cases and is related to the age of the donor and the post mortem time of enucleation. Contraindications, such as transmissible diseases or positive serology (mainly hepatitis B and C), prevent harvested corneas from being transplanted in 4–5% of the cases. Scleral tissue is stored in 70% or 100% ethanol, in glycerol or after freeze drying.
Quality control

Standards for eye banking exist at the Eye Bank Association of America (EBAA) and these have been accepted by the EEBA insofar as they are applicable to the European situation. Also, the EATB has formulated a set of standards for eye banking. A European adverse event reporting system is not yet in place. Various systems for quality assurance and quality control are operative or being developed currently and governments are in the process of installing regulations, such as the licensing of banks or certification.

Allocation criteria

At BIS, for random corneas, a waiting list system is in place. Reasons for priority are primarily contained within the medical urgency of the candidate. In acute cases, for example when perforation has occurred, a cornea will always be available to save the eye. Distribution is also related to the relative number of corneas contributed by the requesting medical centre involved and by the length of the local waiting list. Young recipients have priority for corneas from young donors. When requested by the eye specialist, a recipient is placed on the waiting list for HLA-typed corneas. The allocation rules for this group are based on the matching grade and thereafter on waiting time. A priority is assigned to the candidates who have been waiting longer than 9 months on this list. This may be due to a less frequent HLA phenotype of the recipient. With newer insights in the frequency of distribution of the allotypes, a prognostic index could be developed, predicting the chances of finding a certain degree of match for a given individual, analogous to the current practice in matching for kidney transplantation. The allocation criteria are reviewed annually by an international committee of independent specialists.

New developments

An area of research is the significance of HLA matching in graft survival and several studies, with conflicting outcomes, have been published. It is noteworthy that, for over 20 years, positive effects of HLA-matching have been reported in European studies. This may be related to the fact that homogenous populations, almost always at single centres, were studied in Europe, whereas heterogenous populations were studied in the US and South Africa where ethnic matching was not
performed\textsuperscript{18,21}. Moreover, the reproducibility of the HLA-typing of the recipients is an area of concern\textsuperscript{23}. New prospective, randomized studies are carried out in Europe. BIS is actively involved in two of these studies. The applicability of retinal transplantation or of retinal pigment epithelium (RPE) cells is currently being investigated in animal models in case of retinitis pigmentosa or macular degeneration, which is the most common cause of registered blindness in Western society\textsuperscript{24,25}.

**Heart valve banking**

**Clinical need**

Bio-valves, i.e. human allografts, have their own place as ‘stentless valves’ in heart surgery, in between other therapies, such as the use of mechanical valvular prostheses. Especially for children, the fact that no anticoagulation therapy is needed is of advantage. For adults, the relative resistance to infections make these valves useful for the replacement in case of bacterial endocarditis\textsuperscript{26}. Donated human heart valves are generally used for reconstruction of congenital cardiac malformations, including hypoplastic left heart syndrome, truncus arteriosus, D-transposition of the great arteries with ventricular septal defect and pulmonary stenosis, reconstruction of branch pulmonary arteries, and aortic and pulmonary stenosis and regurgitation. Nowadays, aortic and pulmonary valves are used extensively and in the last few years, the use of mitral valves has also gained new interest\textsuperscript{26,27}. Surgeons can apply various techniques for implantation of donor valves. One of the more complex techniques, with very good clinical results, is the Ross procedure, where the pulmonary valve of the patient is transposed to the aortic site and the original pulmonary valve is replaced by an allograft valve\textsuperscript{28}. Especially in children, the fact that the transposed pulmonary valve retains its capacity to grow is of advantage. Presently, 86 surgeons worldwide perform the Ross procedure at 64 medical centres and 826 patients have been registered\textsuperscript{29}. Since 1986, when the first root replacement of the pulmonary autograft was reported by Ross\textsuperscript{30}, mortality rates have dropped considerably to 1\% (4 out of 401 procedures). Aortic and mitral valves are also harvested and reimplanted\textsuperscript{27,31}. In 1996, 417 valves were allocated through BIS, 256 pulmonary and 161 aortic valves. By the end of 1996, 53 persons were on the waiting list. In Europe, 48 heart valve banks are known to exist, 10 of them are located in the UK and 6 are known to exist in former USSR states\textsuperscript{32}. Of these banks, 25\% dissect 10–50 hearts per year, 12.5\% dissect 50–100 hearts per year and another 12.5\% dissect 100–
250 hearts per year\textsuperscript{32}. Together, the European banks (excluding the UK) and the banks in the former USSR states dissected almost 1750 hearts in 1995, and the banks in the UK almost 1200\textsuperscript{32}. The total production of aortic and pulmonary valves in these countries together was approximately 4500 valves, whereas the number of mitral valves dissected exceeded 100\textsuperscript{32}. Although no specific heart valve bank association exists, they can communicate via the EATB. BIS is involved in efforts to improve communication by organising workshops for heart valve banks at the European level.

**Explantation**

Three sources are available for heart valves: (i) the living, heart beating donor; (ii) the multi-organ, heart-beating donor; and (iii) the non-heart-beating (cadaveric) donor. The relative contribution of these types of donor varies between the regions\textsuperscript{32}. When a heart is donated by a living donor receiving a heart transplantation this is called a 'domino-procedure'. Usually, the explanting surgeon has an understandable tendency to cut close to the aortic valve in a living donor, which makes it more difficult for the implanting surgeon to reimplant the valve in the recipient.

**Preservation, thawing and dilution**

The time elapsed before harvesting, allowed by the banks, without cooling of the body varies between 6–12 h, and with cooling between 12–24 h\textsuperscript{32}. After preparation, inspection and disinfection in a solution with antibiotics at 4°C, the valves are either stored in tissue culture medium and used within 48 h or, as is done in the majority of cases, packed and cryopreserved. Most banks use a controlled rate (1°C/min) freezing procedure to secure optimal preservation of the valve tissue. To achieve this freezing rate in the packed valve, one has to compensate for the release of heat during crystallisation of water. To this end, the freezing curve has to be tailored to the freezing machine, the volume and the packaging of the valve. The object of controlled rate freezing is to limit intra-cellular ice formation, which is detrimental to the cells. With the currently used cryoprotectants, these phenomena play a role, especially in the range from 0 to —40°C, while ice crystals finally stabilize below —130°C. Therefore, valves are stored below —130°C. To prevent remodelling of ice crystals and, therefore, tissue damage, temperature fluctuations of the frozen valve should be avoided.
Similar to the freezing process, during thawing the harmful effects of recrystallisation and osmotic stress is counteracted by cryoprotectants (e.g. DMSO). Since DMSO itself is toxic above 10°C, it has to be diluted and rinsed during thawing, hence the name ‘thawing and dilution’ protocol. Above all, the valves should not be touched during thawing, to prevent the formation of cracks. For the personnel of the operating theatre, responsible for thawing and dilution, instructions should be available that are easily readable in their own language, and preferably of a uniform character.

**Quality control**

Standard operating procedures are important to ensure a high quality level of tissue banking. Controlling the safety of the valves is crucial, as they may transfer transmissible diseases from donor to recipient. Therefore, the traceability of the donor for a given valve is important. Other important issues in quality control are compliance with preformulated specifications of the cryopreservation process. These include, for example, predefined time limits during procurement and during successive stages of processing or specifications of antibiotic solutions used. Furthermore, the description of the valve should inform the surgeon about the fine details of the preparation he is going to use. Since valves are exchanged throughout Europe, this should be done in a standardized way. The EATB involves a section of heart valve banks, which is currently working on a final draft of a standard for heart valve banking.

**Allocation criteria**

Allocation is usually done according to the clinical urgency of the recipient. For BIS, this is indicated by the surgeon. Furthermore, a valve is allocated according to the anatomical characteristics and the waiting time on the list of possible candidates. Although the valves usually have a code, indicating the quality, a key role during allocation is for the picture drawing of the valve, which enables the surgeon to choose the optimal valve for the patient, when available. Some banks store a number of valves at various hospitals in liquid nitrogen tanks, in order to give the surgeons a maximum of freedom at their location (Parker R, personal communication). Other banks prefer that allocation is done in direct communication between the medical authority of the bank and the requesting surgeon. When it comes to transportation, valves are either
transported in a liquid nitrogen container, which is very cumbersome, or on dry ice, at —80°C. Although no definite limits for the duration of the storage time can be given, in general terms the storage time can be longer with colder temperatures. After transferring a valve to —80°C for transportation, several banks advise use of the valve within 1 week, but others allow further storage for up to 3 months. To be on the safe side, BIS advises 1 week.

New developments

Heart valves  HLA matching between donor and recipient has not been practised yet routinely, as the current clinical series without matching indicate a ‘half-life’ of the donor valve of over 15 years. Perhaps in children, where the donor valves degenerate much more rapidly than in adults, HLA matching may have a beneficial effect on durability. Recent research indicates that cryopreserved allografts in children induce a marked HLA alloantibody response within 3 months after surgery, which may cause a deleterious effect on the allograft function. One is, therefore, tempted to contemplate the use of matched allografts or of a short term course of immunosuppressive therapy in these children.

Aortic vessels  Aortic vessels were implanted shortly after explantation during the 1950s, but this method has been abandoned because of relatively poor results with regard to aneurysmatic dilation and an obstruction rate of around 80% within 5 years. With the newer techniques of cryopreservation, a revival of large vessel preservation has occurred and some banks now routinely store the descending part of the thoracic aorta. They are mainly used for replacement of infected artificial prostheses and mycotic aneurysms. The results, so far, have been published with a follow-up time until 42 months. Also, the use of nonvalved homografts of the thoracic aorta is encouraged in operations for complex congenital cardiac diseases. The expectation is that these allografts will have a similar resistance to infection as heart valves reportedly have. BIS cooperates with several banks in Europe which routinely provide these vessels and is also currently developing a procurement protocol.

Veins  From the veins of living donors, as removed during surgery for varicose veins, allografts can be constructed which can be used for access surgery (i.e. dialysis shunts) or bypass surgery in the lower leg, as originally performed from autologous veins. The clinical need in a country such as The Netherlands (approximately 15 million inhabitants)
for these purposes is estimated to be 800–1000 implants per year. In the case of access surgery, the clinical impression is that these shunts are more resistant to infections and suffer less from repeated puncturing. A prospective study to test this hypothesis is currently being performed. In bypass-surgery, a re-enforcing net is added, to counteract formation of aneurysm. For bypass surgery, a specific indication exists where the remaining artery is very fragile, which makes the attachment of the artificial bypass prosthesis (PTFE) very cumbersome. Use of the autologous saphenous vein is preferred, but is not always available. In 1974, the use of specially prepared umbilical cord vein-graft for this purpose was introduced. Several efforts are currently underway to procure and process veins for these purposes in Europe: BIS is involved in one of them.

Bone banking

Clinical need

An increasing demand for allogenic bone and related soft tissue exists in various medical disciplines. Allografts are frequently used in revision of joint arthroplasty and in the reconstructive surgery of the knee. The use of bone grafts is specifically indicated when large skeletal defects following trauma or tumor surgery have to be filled. Also, in dental surgery bone grafts are used to fill lesions. In such cases, demineralized cortical powder or gel is applied which contain proteins with a beneficial action on bone formation. Therefore, bone tissue is transplanted in various forms either unprocessed or processed. It can be used as massive grafts, such as osteo-articular grafts in conjunction with the attached tendons and soft tissue or as intercalary bone. Foreign bone is substituted over a small zone by bone of the recipient, a process called ‘creeping substitution’. Bone banks store various forms of bone depending on the regional clinical need. For the processing of bone, only a few plants are available in Europe, most of them reside in the US. There are numerous places, however, in Europe where bone is stored, although no ‘directory’ of these places is available. Although the total number of bone banks in Europe is unknown, at least 10–15 full-scale bone bank facilities with acceptable standards exist.

Explantation and processing

Bone explantation and processing is time consuming and labour intensive. Explantation is usually done in the operating room under...
aseptic conditions within 24 h of death. Blood samples from the donor are cultured and samples are taken from the bone surface, in order to document the degree and type of bacteriological contamination. Microorganisms of low pathogenicity are cultured from 50% of the grafts, and of high pathogenicity in 3% of the grafts. After explantation, bone grafts are cleaned and frozen, for example according to procedures described by Tomford. Very recently, a new method has been developed, which employs CO$_2$ at high pressure ('supercritical CO$_2$ method'). From spongious bone, chips are made and, from cortical bone, a demineralized powder or gel. The process of demineralization has been claimed to virtually eliminate possible viral contamination. Gamma irradiation may also achieve this at certain levels, although a dose dependent reduction in strengths of the bone has been shown as a side effect. Therefore, since no method can in practice completely inactivate a possible contamination with virus, the donor criteria are very rigorous and the laboratory testing is most extensive in order to reduce the remaining risk for transmissible diseases as much as possible.

**Quality control**

Recently (1997), EATB and EAMST adopted joint standards for bone banking. They call a.o. for the installation of a quality system.

**Allocation criteria**

Allocation criteria are related to medical criteria, as provided by the surgeon. In case of shortage, the region which has provided the donor material is given a certain preference and a waiting list is maintained. In 1996, BIS was involved in the allocation of almost 4000 bone grafts according to these rules.

**New developments**

The banking of femoral heads from living donors (following hip surgery) is increasing, and standards require that these donors be retested for virological diseases 180 days post donation or that PCR tests are done instead. Alternatively, a validated method of viral inactivation can be used. Clinically, these femoral heads are used for the revision of joint arthroplasty or for the production of grounded bonemass, which is applied for the fixation of prostheses.
Middle ear bones are banked in specialized banks for use by the medical specialism involved (ear, nose and throat). These specialists also have an interest in using costal cartilage for implantation in nasal surgery.

**Skin banking**

*Clinical need*

Preserved skin allografts are clinically used as a temporary biologic cover for open wounds. The principal indications are for scald burns and as an overlay for wide meshed autografting. It is used as coverage of excised wounds when an autograft is not available or to improve the condition in poorly vascularized wounds before autografting. In burn wounds, they provide immediate pain relief and give excellent cosmetic results. In 1996, a total of almost 1.3 million cm$^2$ of skin was prepared and issued by the Euro Skin Bank, located at Beverwijk, The Netherlands. This bank was established in 1992, as the successor to the Dutch National Skin Bank, which, in turn, was established in 1976. It cooperates with several skin banks in and outside Europe, for which it processes the skin. It delivers the skin to more than 30 burn centres throughout Europe and sometimes even beyond.

*Explanation*

**Preservation**

Skin was initially preserved using deep-freeze techniques with DMSO, and later glycerol, as a cryoprotective agent. Since 1983, glycerolization instead of cryopreservation became the procedure of choice at the Euro Skin Bank. Glycerol has antimicrobial and antiviral properties and diminishes antigenicity of the tissues, although these findings are still subject of discussion.
Quality control

Standards for skin-banking are developed by the EATB. Several procedures have been adopted for control of the skin preparation and procedures\textsuperscript{62}.

Allocation criteria

Generally, skin is provided to the regions and areas where it is collected from. Working on a large and international scale, however, enables the Euro Skin Bank to reach economies of scale necessary to ‘break-even’ in terms of cost-effectiveness on a non-profit basis\textsuperscript{62}.

New developments

Culturing keratinocytes from the burn patient him/herself could be an ideal solution to improve wound healing and to prevent scar formation\textsuperscript{63}. Currently, skin is spliced enzymatically in 2 layers to provide the optimal matrix. A new development is to remove a second layer of dermis from the donor for this purpose. Currently this is an area of further research.

Summary and conclusions

Tissue banking programmes in Europe are growing in response to an expanding clinical need during the past decade. In many countries, an intermediary is used for procurement and allocation of tissues, which ensures that optimal use is made of scarce tissues without commercialization. Main areas involve the banking of eyes (corneas), heart valves, bone tissue and skin, but many new tissues are being explored, such as the banking of retinal cells, arteries, veins, cartilage and cultured keratinocyte layers. Several associations of tissue banks exists, which are developing standards and thus provide a basis for self regulation and quality assurance. Moreover, new insights in safety aspects for the prevention of transmissible diseases from donor to recipient have led to new concepts in donor screening. Thus minimum requirements have been formulated to screen the medical history and the serum for risk factors. In particular, the use of PCR techniques to demonstrate viral nucleic acids may become helpful in decreasing the so-called ‘window-phase’, during which a donor can be infectious but no antibodies can be
demonstrated. In the light of the existing international regulations for
blood transfusions, it is quite disappointing, however, that no such
equivalent regulation of tissues exists in Europe. Several countries have
national regulations but, until now, no EU Directive has been developed
concerning the safety, quality and non-commercial allocation of human
tissues. The need for such regulation may be apparent.

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References

1 AATB. Information Alert 1996; 4: 5–8
2 Revised EAMST/EATB standards for tissue banking. 1997
3 Revised Canadian General Standard on Safety of Organs and Tissues for transplantation, 1996
   (draft)
4 Medical Standards of the Eye Bank Association of America, 1995
5 Hughes JM, Jaffe HW Guidelines for preventing transmission of human immunodeficiency
   virus through transplantation of human tissue and organs. Morb Mortal Wkly Rep 1994; 43:
   RR-8
6 Klintmalm GB Regulation of organ donation in the United States. Chimera 1996; 8: 14–7
7 LeFor WM, McGonigle AF, Wright CE, Shires III DL. The frequency of false positive HbsHG
   screening test result with cadaveric tissue donors is dependent upon the assay procedure used.
   Tissue Cell Rep 1996; 1: 6–8
8 Novick SJ, Schrager JA, Nelson JA, Anderson ME, Baskin BL. Comparison of two hepatitis B
   surface antigen and two HIV-1 (p24) antigen EIA test kits with hemolyzed cadaveric blood
   specimens. Transplant Proc 1996; 5: 292:5-26
9 Koopman-van Gemert AWMM. Hemodilution, what is right? Transplant Proc 1996; 28 2934–

10 Burtonboy G, Delloye C. Polymerase chain reaction in cadaveric blood and tissue. Transplant Proc 1996; 28: 2927-8
11 Colucci G. Development of polymerase chain reaction diagnostic assays for the detection and quantitation of human immunodeficiency virus and hepatitis C virus genomes. Transplant Proc 1996; 28: 2929-30
23 Hopkins KA, Maguire MG, Fink NE, Bias WB. Reproducibility of HLA-A, B, and DR typing using peripheral blood samples: results of retyping in the collaborative corneal transplantation studies. Hum Immunol 1992; 33: 122-8
24 Bird AC. Pathogenesis of retinal pigment epithelial detachment in the elderly; the relevance of Bruch's membrane change. Eye 1991; 5: 1-12
35 Szilagyi DE, Rodriguez FJ, Smith RF, Elliott JP. Late fate of arterial allografts. *Arch Surg* 1970; 101: 721-33
61 Mackie DP. The Euroskinbank: development and application of glycerol-preserved allografts. *J Burn Care Rehabil* 1996, 18: S7-S9
62 De Backere ACJ. Euro Skin Bank: large scale skin-banking in Europe based on glycerol-preservation of donor skin. *Burns* 1994; 20: S4-S9